Parent Prediction of Autism Spectrum Disorder in Infants At Risk: A Follow-up Study

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Abstract

Later-born siblings of children with autism spectrum disorder (ASD) are considered at biological risk for ASD and the broader autism phenotype. Early screening may detect early signs of ASD and facilitate intervention as soon as possible. This follow-up study revisits and re-examines a second-degree autism screener for children at biological risk of autism, the Parent Observation Early Markers Scale (POEMS, Feldman et al., 2012). Using available follow-up information, 110 children (the original 108 infants plus 2 infants recruited after the completion of the original study) were divided into three groups: diagnosed group (n = 13), lost diagnosis group (n = 5), and undiagnosed group (n = 92). The POEMS continued to show acceptable predictive validity. The POEMS total scores and mean number of elevated items were significantly higher in the diagnosed group than the undiagnosed group. The lost diagnosis group did not differ from the undiagnosed group on POEMS total scores and elevated items at any age, but the lost diagnosis group had significantly lower total scores and number of elevated items than the diagnosed group starting at 18 months. Both ASD core and subsidiary behaviours differentiated the diagnosed and undiagnosed groups from 9–36 months of age. Using 70 as a cut-off score, sensitivity, specificity, and positive predictive value (PPV) were .69, .84, and .38, respectively. The study provides further evidence that the POEMS may serve as a low-cost early screener for ASD in at risk children and pinpoint specific developmental and behavioural problems that may be amenable to very early intervention.

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Extended Introduction

Format of this Thesis

The layout of this thesis is slightly different from the traditional thesis layout. We have included an extended introduction to provide a more in-depth literature review and a more detailed research gap description. Then, a manuscript for submission to a peer-review journal is embedded in the middle of the thesis with the study method, results, discussion and conclusion. Hence, there is some redundancy between the Extended Introduction of the thesis and the introduction found in the manuscript. The manuscript uses APA (sixth edition) style and, although it follows an extended thesis introduction, is formatted as a stand-alone document..

Purpose of the Study

Later-born siblings of children with autism spectrum disorder (ASD) are considered at biological risk for ASD (Clifford et al., 2013; Feldman et al., 2012; Messinger et al., 2013; Rozga et al., 2011). Studies have shown that it is critical for children with ASD to receive behavioural intervention as early as possible (Virues-Ortega, Rodríguez, & Yua, 2013). However, despite growing evidence that symptoms of ASD may start to show in the first two years of life (and even before the age of 1 year), diagnosis usually happens later in childhood (Lemcke et al., 2013). Given the fact that parents are closest to their children, a parent-report type of screener could closely monitor the development of at-risk infants to detect early signs of ASD at as young an age as possible (Feldman et al, 2012; Ghuman et al, 2011). The purpose of this study was to continue the work of Feldman et al. (2012) on the Parent Observation of Early Markers Scale (POEMS) to determine how accurately parents of at-risk infants detect early signs

of ASD and which signs at what child ages distinguish at risk infants subsequently diagnosed from those not diagnosed with ASD. Identification of early ASD signs may lead to earlier diagnosis and intervention, and may even lead to prevention strategies implemented prior to diagnosis. The following literature review will provide a summary of the characteristics of ASD, current status of research on at-risk infants, and available broadband and ASD-specific screeners.

Autism Spectrum Disorder (ASD)

Diagnosis. ASD is a common neurodevelopmental disorder with increasing prevalence and a substantial impact on the individuals with ASD and their families. The latest version of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM 5, American Psychiatric Association [APA], 2013), puts ASD as a single category with two domains and three levels. The two domains are "social communication deficits" and "fixated interests and repetitive behaviors." The three levels are for diagnosing the severity of ASD symptoms: level 1 (mild), level 2 (moderate), and level 3 (severe) (APA, 2013).

Prevalence. The rate of ASD occurrence has dramatically increased in the past 30 years (Windham et al., 2011). U.S. Centers for Disease Control and Prevention announced a current rate of 1 in 68 children diagnosed with ASD (Baio, 2014) which is raised from 1 in 110 in 2012 (Baio, 2012). The 2014 prevalence rate is 1.47%. Another study in South Korea showed an astonishingly high rate of 2.6% while other studies in different countries throughout the world, including China, Israel, and the United Kingdom, have all shown steady increases for the last few decades (Davidovitch, Hemo, Manning-Courtney, & Fombonne, 2013).

Etiology. The cause of ASD is still not clear but many studies show that it involves both genetic and environmental factors (Giannandrea et al, 2010; Hallmayer et al, 2011). Theories include genetic inheritance (Landrigan, Lambertini, & Birnbaum, 2012), epigenetic modification

(Grafodatskaya, Chung, Szatmari, & Weksberg, 2010) and exposure to chemicals (Grafodatskaya et al, 2010, Gropman & Batshaw, 2010; Hartzell & Seneff, 2012). Over 80,000 new synthetic chemicals in the past 50 years have been introduced to the environment, all of which have the potential to be toxic to children and pregnant women (Landrigan et al., 2012). One controversial factor has been disproved: Dr. Wakefield's research linking Measles, Mumps and Rubella (MMR) vaccine to ASD was proved fraudulent by the British Medical Journal (Deer, 2011).

At Risk Infants

Younger siblings of children with ASD have a higher chance of ASD diagnosis than other populations (Clifford et al., 2013; Feldman et al., 2012; Rozga et al., 2011). Research shows that this population has a high rate (10%-20%) of ASD diagnosis or ASD characteristics (broader phenotype) compared with other children (close to 1%) (Bolton, Golding, Emond, & Steer, 2012; Pierce et al., 2011; Warren et al., 2012). Since the etiology of ASD may combine genetic and environmental factors, it is very likely that a biological younger sibling of a child with ASD will share similar genetic and environmental conditions. Many studies have been conducted on infants at risk for ASD. To avoid the limitations of retrospective studies such as recall mistakes or parental bias (Jones, Gliaga, Bedford, Charman, & Johnson, 2014), only prospective studies are reviewed here. One recent meta-analysis (Jones et al., 2014) that reviewed 42 prospective studies is described below. Then other recent and relevant studies not included in that meta-analysis are outlined briefly.

Jones et al. (2014) reviewed 42 prospective studies of infants at risk. The purpose of the review was to identify early ASD behaviour patterns through examining the first two years of life of infants at risk. The paper discussed the behavioral symptoms of ASD that may emerge

before a child turns 2 years old, but included studies covering infants up to 36 months. The authors organized the information from all the studies into four sections: (1) social interaction, (2) communication, (3) restrictive and repetitive behaviours, and (4) other symptoms. The authors argued that studying behaviours of infants at risk could provide critical information on early autistic symptoms, and aid in the development of methods to screen all children at high risk of ASD at an early age.

Jones and colleagues (2014) reported that children who were later diagnosed with ASD at the age of 24 or 36 months show very little difference compared to typical development (TD) children in initiating normal engagement of social interaction with their mothers at the age of 6 months. Social interaction skills such as gaze direction (i.e., following parents' eyes or their pointing) begin to differ after 12 months of age for infants at risk who eventually developed ASD compared to at-risk not diagnosed, and non-at-risk infants.

It is common for children with ASD to have difficulties in both receptive and expressive aspects of vocal communication. The delay in developing basic verbal skills is considered as a major risk factor of ASD development in infants at risk (Jones et al., 2014). While restrictive and repetitive behaviours are a defining feature of ASD (APA, 2013), they are common in the first year of life in all children. However, these behaviours typically decrease significantly between one and two years of age and further reduce at around four years, except in children with ASD (Stone, Coonrod, & Ousley, 2000). Few studies have found differences in restrictive and repetitive behaviours in infants at risk compared to non-risk infants (Jones et al., 2014). As Feldman et al. (2014) pointed out, it may be because parents do not perceive such behaviours as abnormal or problematic because many infants demonstrate them. However, one laboratory-

based study showed that among 47 different repetitive behaviours, 12–18 month old infants at risk for ASD showed higher hand-waving frequency then non-risk children (Loh et al., 2007).

Other features currently not included in diagnostic criteria of ASD might provide an insight to ASD development in at risk infants. Early executive function capabilities consist of the comparison of typical development of goal-directed behaviours such as disengagement. Although no specific research was done with such a focus, several studies have found that at around 12–14 months, children who are later diagnosed with ASD show increased latency of disengaging or shifting in attention (Landry & Bryson, 2004; Johnson, Gillis, & Romanczyk, 2012). Motor development can often be a relatively high strength for children with ASD. However, studies have found atypicalities in the coordination of gross and fine motor skills near the second year of life for children who were later diagnosed with ASD (Bhat et al., 2011; Fournier et al., 2010). Other problem behaviours such as eating and sleep disturbances, and tolerance to waiting and transitions, typically seen in children with ASD, may also differentiate infants at risk for ASD eventually diagnosed from infants at risk not diagnosed (Feldman et al., 2012) and low-risk infants (Feldman et al., 2014).

Messinger et al. (2013) conducted a comprehensive, large sample size study to examine ASD-related characteristics in 507 high-risk (HR) infants (infants from families with ASD histories) without an ASD diagnosis at the age of 3 years by comparing the outcomes to a same age control group of 324 low-risk (LR) infants (infants from families without ASD histories). Results showed that high or average developmental quotient (DQ) in the presence of low or elevated ASD severity characterized 79% of HR infants. However, 21% of HR infants had low or low-average DQ in the presence of low or elevated ASD severity. In conclusion, the

percentage of the HR infants who have a chance to develop ASD or a broader autism phenotype was found to be higher in the Messinger et al. (2013) study than previous studies.

Lemcke et al. (2013) conducted a large-scale longitudinal study to identify possible early signs of ASD within the Danish National Birth Cohort. The study separated participants into four groups: typical, ASD, Child Autism (CA), and Intellectual Disability (ID) no ASD, and analyzed the differences based on the phone interview with the mothers when the infants were 6 and 18 months old. In total, 76,441 children participated in the study (65,782 for the 6-month interview and 62,721 for the 18-month interview). Based on the data collected, the study indicated that there were parent-observed differences in their development on motor, emotion and comprehension skills among the four groups. Although there was little difference at the 6 months interview, the differences increased at follow-up studies at 18 months. Among all predictor groups (social and language, cognitive, and motor function) used in the study, ID no ASD showed most differences followed by the CA and ASD group.

In conclusion, it is important to closely monitor these children from birth (Feldman et al., 2012). With core and subsidiary symptoms of ASD such as, but not limited to, easily distressed temperament, disengagement with social interaction cues, delayed behavioural development compared to other peers, sometimes being observed in the first year of life in at risk infants (Clifford et al., 2013; Feldman et al., 2012; Feldman et al., 2014; Ghuman, Leone, Lecavalier & Landa, 2011; Guinchat et al., 2012; Hutman, Chela, Gillespie-Lynch & Sigman, 2012; Rozga et al., 2011; Wan et al., 2012), early identification could lead to earlier intervention to reduce or eliminate the symptoms of ASD. Therefore, a close monitoring system for infants at risk for ASD is necessary.

Screening Instruments for ASD

Eleven broadband and ASD-specific screeners are reviewed. These screeners were selected for review if they were published after the Feldman et al. (2012) review, were not reviewed in Feldman et al. (2012) or had a research update after being reviewed in Feldman et al. (2012). As can be seen in the reviews below, the recent trend is to use broadband screeners to filter out non/low-risk infants, and then use ASD-specific screeners to increase predictive validity. The reasoning for this trend is to be able to differentiate ASD from other developmental disabilities in high-risk infants and to decrease the possibility of false positive observations (Ben-Sasson, Habib, & Tirosh, 2014; Matson, Wilkins, & Fodstad, 2011).

Broadband screeners only. Broadband screeners are used to detect developmental problems in general, and so they may not differentiate ASD from other developmental disabilities. Two widely used broadband screeners are reviewed.

Communication and Symbolic Behavior Scales Developmental profile Infant-Toddler Checklist **(**CSBS-DP-ITC: Wetherby, Brosnan-Maddox, Peace, & Newton, 2002**).** Pierce et al. (2011) used the CSBS-DP-ITC with a one-year check-up approach to be able to identify ASD, language delay (LD), and developmental delay (DD) as early as 12 months of age. The CSBS-DP-ITC correctly identified 133 children who showed developmental disorders (32 ASD, 56 LD, 9 DD, and 36 other) resulting in an acceptable Positive Predictive Value (PPV) of 75%. However, the prerequisite of requiring all pediatricians to attend a training seminar and spend time completing the form could reduce the likelihood of its use in practice.

Child Behavior Checklist **(**CBCL: Achenbach, 1978**).** The CBCL is a 100-item parent-report measure that has mostly been used with children and adolescents between 4-18 years for a broad range of behavior and emotional problems (Narzisi et al, 2013). It was first tested for ASD

identifying ability for young children with 141 children between 18-36 months (47 with ASD, 47 with other psychiatric disorders (OPD), 47 with typical development (TD) (Narzisi et al in 2013). The result showed that the CBCL 1 ½ - 5 (years) had reasonable sensitivity (.85) and specificity (.83) when discriminating ASD from OPD. In another study involving the CBCL by Myers, Gross and McReynolds (2013), they found that the CBCL had excellent sensitivity (.93) but poor specificity (.29) and PPV (.51) with a low cut-off score (65), and therefore questioned the ability of CBCL to distinguish ASD from other developmental disabilities. Thus, more studies are needed to evaluate the CBCL 1 ½ - 5.

Broadband Screeners Combined with Another Screener

Parents' Evaluation of Developmental Status **(**PEDS: Glascoe, 1997**).** The PEDS is a 10-item parent-report measure for children from newborn to eight years of age with developmental concerns. Roux et al. (2012) used the PEDS for all children aged < 5 years and as well the Modified Checklist for Autism in Toddlers (M-CHAT: Robins et al., 2001) for children aged 16-48 months to screen children with developmental delay for possible ASD. Of the 2,896 children, the PEDS identified 56% of total with moderate to high risk for developmental delay while the M-CHAT identified 21% of total with high risk for ASD. However, the study did not provide follow-up information regarding any ultimate diagnoses for these children. Therefore, the predictive values of using the combined the PEDS and the M-CHAT are not available. Moreover, the method used in the study required considerable resources (training pediatricians); that has made it difficult for other researchers to replicate the study or to use in general practice.

Eapen et al. (2014) used the PEDS as a first stage screener and the M-CHAT in the second stage in two daycares: one is a specialized daycare for infants and children with ASD or other developmental or learning disabilities, and the other one is a regular daycare. The intent of the

study was to see if the results from the PEDS would be able to predict the findings from the M-CHAT in a meaningful manner. They found that the adjusted sensitivity of the PEDS was .65 when using the cut-off score of 4 or more. The results suggested that the PEDS was not a very effective level 1 ASD screener. From these recent PEDS studies, we can conclude that it is recommended to use the PEDS with a second stage screener, recognizing that this approach could require more work for the professionals and the families.

ASD-specific screeners alone. ASD-specific screeners are designed to identify symptoms of ASD in children who may develop ASD. Screeners using parents report may have an advantage as being more cost-effective and easily-accessible than instruments requiring trained professionals (Feldman et al., 2012; Ghuman et al., 2011).

Childhood Autism Rating Scale **(**CARS: Schopler, Reichler, DeVellis, & Daly, 1980). The CARS is a widely used and well-studied screener for children ≥ 18 months old using a one-to-one interview approach involving trained professionals (Geier, Kern, & Geier, 2013; Mayes et al., 2009). It has promising results in distinguishing ASD from other developmental disorders, but not ASD levels. Nah et al. (2014) found that using the CARS as a secondary screening method to analyse 55 children aged 9–42 months yielded acceptable sensitivity (.83) two years after the initial assessment, but the sensitivity was lower in the 6-year follow-up study (.64).

Young Autism and other Developmental Disorders CHeckup Tool **(**YACHT-18, Honda & Shimizu, 2002)**.** In order to increase the sensitivity of the YACHT-18, Honda et al. (2009) conducted a study combining the trained professionals with the Extraction and Refinement (E&R) Strategy. The extraction stage involved using the YACHT-18 to screen 18 month old children with concerns for ASD. The refinement stage involved conducting follow-ups including telephone call, home visit, psychological consultation and weekly group to ensure referrals. The

extraction stage takes into account all children showing even the slightest sign of ASD to minimize false negatives and reduce false positives in the Refinement stage. The results showed that " sensitivity was 60% for autistic disorder and 82.6% for developmental disorders. Specificity for developmental disorders rose to 100% with the E&R Strategy" (Honda et al. 2009, p. 972). E&R effectively increased the predictive values of the YACHT-18, but also increased the cost and complicated the research due to the complex follow-up procedure.

Checklist for Early Signs of Developmental Disorders **(**CESDD: Dereu et al., 2010). Dereu et al. (2010) developed a 25-item child-care-worker report screener. After lowering the cut-off scores from >4 signs in children older than 12 months to > 2 signs for all children, sensitivity increased from .68 to .80, specificity remained about the same (.96 to .94), as did PPV(.10 to .07). Dereu et al. (2010) recommended using the CESDD with further assessments to lower false positive values.

Brief Infant-Toddler Social and Emotional Assessment (BITSEA: Briggs-Gowan & Carter, 2002). The BITSEA is a 42-item parent-report screener given to parents during their paediatric visits for children aged 12−36 months with social-emotional concerns. BITSEA had acceptable sensitivity (.95) and specificity (.68) in this study (Briggs-Gowan et al., 2004). Gardner et al. (2013) used 17 ASD items from the 42 BITSEA items that they called a "Total ASD" screening cut-off score. Using Total ASD cut-off scores of 12.00 or 11.00, they found that the 17-item BITSEA had acceptable predictive validity: sensitivity of .76 or .73 and specificity of .71 or .80. However, neither Briggs-Gowen et al. (2004) nor Gardner et al. (2013) obtained actual ASD diagnoses; they compared the scores to CBCL/1.5−5 (Achenbach & Rescorla, 2000) and M-CHAT (M-CHAT: Robins et al., 2001), respectively.

Modified Checklist for Autism in Toddlers (M-CHAT: Robins et al., 2001). The M-CHAT is a commonly used screener (Narzisi et al., 2013; Sunita & Bilszta, 2013). Sunita and Bilszta (2013) reported that the M-CHAT may be biased due to inclusion of early intervention population groups in the calculation of predictive values. Scarpa et al. (2013) found that show that participants with low maternal education and minority status were more likely to endorse items suggestive of ASD and concluded that there was poor internal inconsistency in these samples used. Thus, the generalizability of the M-CHAT needs more research.

Autism Observation Scale for Infants (AOSI, Zwaigenbaum et al., 2005). The AOSI is an 18-item clinician observation measuring tool designed specifically for infants at risk for ASD between the ages of 6 and 18 months. Bryson & Zwaigenbaum (2014) revisited the AOSI to determine its feasibility as a screener for infants with no family history of ASD. The result suggested that the AOSI is a reliable method for finding and observing ASD related behaviours in infants from 6 to 18 months old (Bryson & Zwaigenbaum, 2014). Nevertheless, the sensitivity of the AOSI was unsatisfactory (Ben-Sasson & Carter, 2012; Bryson & Zwaigenbaum, 2014). The low sensitivity was mainly concentrated on groups of children with high verbal skills or mild symptoms of ASD, even though they were diagnosed with ASD later at the age of 3 years. Furthermore, the AOSI also picked up symptoms similar to ASD on some children who were not later diagnosed with ASD.

ASD-Specific Second-Order Screeners Using Infants at Biological Risk

ASD-specific second-order screeners are designed specifically for infants at risk or were initially validated with this group. Given the fact that this population has a higher chance of developing ASD or a broader autism phenotype than the general population (Feldman et al.,

2012; Messinger et al., 2013), it is important to have screener instruments that are validated with infants at risk.

First Year Inventory **(**FYI: Reznick et al., 2007) and ***First Year Inventory–Retrospective*** (FYI-R: Watson et al., 2007). The FYI and the FYI-R are parent-report measures designed for at risk infants at the age of 12 months. However, the FYI was not tested for any of the predictive values so further validation of the screener is needed. The FYI-R had acceptable predictive values, but because the parents completed the questionnaire retrospectively, prospective rates of sensitivity and specificity are unknown. Ben-Sasson and Carter (2012) conducted a study in Israel comparing the FYI with the AOSI (Zwaigenbaum et al., 2005) and the Mullen Scales of Early Learning (Mullen, 1995) with 17 at-risk children and 38 low-risk infants. The authors found that the FYI showed similar detection results in the social-communication areas as the AOSI and was further verified by the language results of Mullen Scale. Ben-Sasson, Habib, and Tirosh (2014) found similar results to Ben-Sasson and Carter (2012) using the First Year Inventory–Lite, which is an abbreviated version of the original FYI (24 vs. 63 questions, respectively).

Parent Observation of Early Markers Scale (POEMS: Feldman et al., 2012, Appendix D). Feldman et al. (2012) identified a research gap: there was no valid early screener relying exclusively on parent report and including a range of ASD-specific symptoms and related behaviours in the first year of life. To fill the gap, Feldman and associates created the POEMS designed to efficiently identify ASD for later-born siblings of children with ASD (Feldman et al., 2012)**.** Consisting of 61 items, the POEMS is designed to be a simple and low-cost tool that can help parents to detect early signs of ASD and collateral behaviours often seen in young children with ASD, so as to access required services as early as possible. In the preliminary study

(Feldman et al., 2012), the families recruited had at least one biological child with an independent diagnosis of ASD, and a younger biological sibling. In total, 108 infants participated in the original study (including one set of identical twins and one set of non-identical twins). The POEMS had acceptable psychometric properties (internal consistency, test-retest reliability and construct validity) and predictive validity. By the end of the original prospective study, a total of nine children (6 males, 3 females) had received independent community diagnoses of ASD by 3 years of age. The POEMS differentiated the subsequently diagnosed from the undiagnosed at risk infants as early as 9 months of age. As diagnosis was determined at 3 years of age, it is possible that more children were diagnosed after this age. Hence, the follow-up study described in this thesis examined the POEMS predictive validity with children from the original sample who were or were not diagnosed with ASD both before and after age 3 years.

Filling the Gaps

In conclusion, there has been rapid development of screeners for early ASD detection and of screener tool use for infants at risk. Other than the POEMS, none of the newer early detection research is a parent-report screener that is easy to use and capable of detecting early signs of core and commonly seen features of ASD at less than 12 months of age in at risk infants, Therefore, the POEMS holds promise as a screening tool parents can use to monitor ASD symptoms and related developmental and behaviour problems in younger siblings of children with ASD. However, Feldman et al. (2012) reported POEMS scores only up to 24 months and only followed at-risk children up to the age of 36 months; nine of these children were diagnosed with ASD. This follow-up study was designed to extend the POEMS findings.

Studies have shown that later-diagnosed at-risk infants do not show differences at the age of 6 months from undiagnosed at-risk infants (Feldman et al., 2012) and from low-risk infants

(Feldman et al., 2014), but social-communication deficit could be detected around the age of 12 months (Ghuman et al., 2011; Guinchat et al., 2012; Hutman et al., 2012; Rozga et al., 2011; Wan et al., 2012;). Feldman et al. (2012) found behavioural differences—mostly in social and communicative development, but also in collateral behaviours like sleep and eating problems—in the POEMS scores between subsequently diagnosed and undiagnosed at-risk infants as early as 9 months of age. Feldman et al. (2014) showed similar early differences between at-risk and low-risk infants. Thus, the POEMS could provide data to help determine the starting time of such differences since the tool is designed to be filled out on a monthly basis from the age of 1 month.

The POEMS has items covering the core ASD areas (problems in social-communication development, restricted interests, and repetitive behaviours), in addition to behaviour problems often seen in young children with ASD (e.g., eating, sleeping, waiting, tolerance issues) that parents would be likely to notice and be concerned about (Cotton and Richdale, 2010; Emond et al., 2010). If these early collateral behaviours are predictive of later ASD diagnosis, clinicians will have more evidence to start pre-diagnostic preventative interventions. This follow-up study updates the ASD diagnosis of the original POEMS sample (some of whom were up to 13 years old). This study also compares 1–36 month POEMS scores in at risk infants who lost their ASD diagnosis to at risk children who kept their diagnosis and those not diagnosed

Research Questions and Hypothesis

Two research questions were identified. 1. Is POEMS as an ASD-specific second-order screener of at risk infants able to differentiate the following three diagnostic groups before diagnosis: diagnosed with ASD, never diagnosed with ASD, and diagnosed with ASD then lost

the diagnosis? 2. Which behaviours differentiate the three groups at different ages up to 36 months? The first question was addressed through testing the following hypotheses:

1. The “diagnosed with ASD” group will have higher POEMS scores and more elevated items than the “lost diagnosis” group and “undiagnosed” group.
2. The “lost diagnosis” group will have higher POEMS scores and more elevated items, than the “undiagnosed” group.

The next section is a draft manuscript for submission for publication in a peer review journal. Note that the submission will have multiple authors (long-time investigators of the ASD-CARC prospective study), but the MA candidate will be lead author, and solely wrote the manuscript portion of the thesis, below (with feedback from the supervisor). Parts from the above introduction will be repeated in the draft manuscript, below. The Method, Results, Discussion, and Conclusion sections for both the thesis and the manuscript are provided within the manuscript sections.

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Draft Manuscript

Parent Prediction of Autism Spectrum Disorder in Infants at Risk: A Follow-up Study

Abstract

Later-born siblings of children with autism spectrum disorder (ASD) are considered at biological risk for ASD and the broader autism phenotype. Early screening may detect early signs of ASD and facilitate intervention as soon as possible. This follow-up study revisits and re-examines a second-degree autism screener for children at biological risk of autism, the Parent Observation Early Markers Scale (POEMS, Feldman et al., 2012). Using available follow-up information, 110 children (the original 108 infants plus 2 infants recruited after the completion of the original study) were divided into three groups: diagnosed group (n = 13), lost diagnosis group (n = 5), and undiagnosed group (n = 92). The POEMS continued to show acceptable predictive validity. The POEMS total scores and mean number of elevated items were significantly higher in the diagnosed group than the undiagnosed group. The lost diagnosis group did not differ from the undiagnosed group on POEMS total scores and elevated items at any age, but the lost diagnosis group had significantly lower total scores and number of elevated items than the diagnosed group starting at 18 months. Both ASD core and subsidiary behaviours differentiated the diagnosed and undiagnosed groups from 9–36 months of age. Using 70 as a cut-off score, sensitivity, specificity, and positive predictive value (PPV) were .69, .84, and .38, respectively. The study provides further evidence that the POEMS may serve as a low-cost early screener for ASD in at risk children and pinpoint specific developmental and behavioural problems that may be amenable to very early intervention.

Parent Prediction of Autism Spectrum Disorder in Infants At Risk: A Follow-up Study

Introduction

Need for Early ASD Screening

Later-born siblings of children with autism spectrum disorder (ASD) are considered at biological risk for ASD**,** with up to 20% being diagnosed or showing the broader autism phenotype (Clifford et al., 2013; Feldman et al., 2012; Messinger et al., 2013; Rozga et al., 2011). Vulnerability to ASD likely involves genetic, epigenetic and environmental interactions (Jones et al., 2014). Studies have shown that it is critical for children with ASD to receive behaviourally based intervention as early as possible (Virues-Ortega, Rodriguez, & Yua, 2013). However, despite growing evidence that symptoms of ASD may start to show in the first two years of life, diagnosis usually happens later in childhood (Lemcke et al., 2013). Given the fact that parents are closest to their children, a parent-report type of screener could closely monitor the development of at risk infants to detect early signs of ASD at the youngest possible age (Feldman et al., 2012; Ghuman et al., 2011).

ASD Screener

Eleven broadband and ASD-specific screeners are reviewed. These screeners were selected for review if they were not reviewed in, were published after, or had a research update after being reviewed in Feldman et al. (2012), As can be seen in the reviews below, the recent trend is to use broadband screeners to filter out non/low-risk infants, and then use ASD-specific screeners to increase predictive validity. The reasoning for this trend is to be able to differentiate ASD from other developmental disabilities in high-risk infants and to decrease the possibility of false positive observations (Ben-Sasson, Habib, & Tirosh, 2014; Matson, Wilkins, & Fodstad, 2011).

Broadband screeners only. Broadband screeners are used to detect developmental problems in general, but they may not differentiate ASD from other developmental disabilities. Three widely used broadband screeners are reviewed.

Communication and Symbolic Behavior Scales Developmental profile Infant-Toddler Checklist (CSBS-DP-ITC: Wetherby, Brosnan-Maddox, Peace, & Newton, 2002). Pierce et al. (2011) used the CSBS-DP-ITC with a one-year check-up approach to be able to identify ASD, language delay (LD), and developmental delay (DD) as early as 12 months of age. The CSBS-DP-ITC correctly identified 133 children who showed developmental disorders (32 ASD, 56 LD, 9 DD, and 36 other) resulting in an acceptable Positive Predictive Value (PPV) of 75%. However, the prerequisite of requiring all pediatricians to attend a training seminar and spend time completing the form could reduce the likelihood of its use in practice.

Child Behavior Checklist (CBCL: Achenbach, 1978). The CBCL is a 100-item parent-report measure that has mostly been used with children and adolescents between 4-18 years for a broad range of behavior and emotional problems (Narzisi et al, 2013). It was first tested for ASD identifying ability for young children with 141 children between 18-36 months (47 with ASD, 47 with other psychiatric disorders (OPD), 47 with typical development (TD) (Narzisi et al in 2013). The result showed that the CBCL 1 ½–5 (years) had reasonable sensitivity (.85) and specificity (.83) when discriminating ASD from OPD. In another study involving the CBCL by Myers, Gross and McReynolds (2013), they found that the CBCL had excellent sensitivity (.93) but poor specificity (.29) and PPV (.51) with a low cut-off score (65), and therefore questioned the ability of the CBCL to distinguish ASD from other developmental disabilities. Thus, more studies are needed to evaluate the CBCL 1 ½–5.

Broadband Screeners Combined with Another Screener

Parents' Evaluation of Developmental Status **(**PEDS: Glascoe, 1997). The PEDS is a 10-item parent-report measure for children from newborn to eight years of age with developmental concerns. Roux et al. (2012) used the PEDS for all children aged < 5 years and as well the Modified Checklist for Autism in Toddlers (M-CHAT: Robins et al., 2001) for children aged 16-48 months to screen children with developmental delay for possible ASD. Of the 2,896 children, the PEDS identified 56% of total with moderate to high risk for developmental delay while the M-CHAT identified 21% of total with high risk for ASD. However, the study did not provide follow-up information regarding any ultimate diagnoses for these children. Therefore, the predictive values of using the combined the PEDS and the M-CHAT are not available. Moreover, the method used in the study required considerable resources (training pediatricians); that has made it difficult for other researchers to replicate the study or to use in general practice.

Eapen et al. (2014) used the PEDS as a first stage screener and the M-CHAT in the second stage in two daycares: one is a specialized daycare for infants and children with ASD or other developmental or learning disabilities, and the other one is a regular daycare. The intent of the study was to see if the results from PEDS would be able to predict the findings from the M-CHAT in a meaningful manner. They found that the adjusted sensitivity of the PEDS was .65 when using the cut-off score of 4 or more. The results suggested that the PEDS was not a very effective level 1 ASD screener. From these recent PEDS studies, we can conclude that it is recommended to use PEDS with a second stage screener, recognizing that this approach could require more work for the professionals and the families.

ASD-specific screeners alone. ASD -specific screeners are designed to identify autistic ASD symptoms in children who may develop ASD. Screeners using parents report may have an

advantage as being more cost-effective and easily-accessible than instruments requiring trained professionals (Feldman et al., 2012; Ghuman et al., 2011).

Childhood Autism Rating Scale (CARS: Schopler, Reichler, DeVellis, & Daly, 1980). The CARS is a widely used and well-studied screener for children ≥ 18 months old using a one-to-one interview approach involving trained professionals (Geier, Kern, & Geier, 2013; Mayes et al., 2009). It has promising results on distinguishing ASD from other developmental disorders, but not ASD levels. Nah et al. (2014) found that using the CARS as a secondary screening method to analyse 55 children aged 9-42 months yielded acceptable sensitivity (.83) two years after the initial assessment, but was lower in the 6-year follow-up study (.64).

Young Autism and other Developmental Disorders CHeckup Tool (YACHT-18, Honda & Shimizu, 2002). In order to increase the sensitivity of the YACHT-18, Honda et al. (2009) conducted a study combining the trained professionals with the Extraction and Refinement (E&R) Strategy. The extraction stage involved using the YACHT-18 to screen 18 month old children with concerns for ASD. The refinement stage involved conducting follow-ups including telephone call, home visit, psychological consultation and weekly group to ensure referrals. The extraction stage takes into account all children showing even the slightest sign of ASD to minimize false negatives and reduce false positives in the Refinement stage. The results showed that " sensitivity was 60% for autistic disorder and 82.6% for developmental disorders. Specificity for developmental disorders rose to 100% with the E&R Strategy" (Honda et al. 2009, p. 972). E&R effectively increased the predictive values of the YACHT-18, but also increased the cost and complicated the research due to the complex follow-up procedure.

Checklist for Early Signs of Developmental Disorders (CESDD: Dereu et al., 2010). Dereu et al. developed a 25-item child-care-worker report screener. After lowering the cut-off scores

from > 4 signs in children older than 12 months to > 2 signs for all children, sensitivity increased from .68 to .80, specificity remained about the same (.96 to .94), as did PPV (.10 to .07). Dereu et. al., (2010) recommended using the CESDD with further assessments to lower false positive values.

Brief Infant-Toddler Social and Emotional Assessment (BITSEA: Briggs-Gowan & Carter, 2002). The BITSEA is a 42-item parent-report screener given to parents during their paediatric visits for children aged 12–36 months with social-emotional concerns. The BITSEA had acceptable sensitivity (.95) and specificity (.68) in this study (Briggs-Gowan et al., 2004). Gardner et al. (2013) used 17 ASD items from the 42 BITSEA items that they called a "Total ASD" screening cut-off score. Using Total ASD cut-off scores of 12.00 or 11.00, they found that the 17-item BITSEA had acceptable predictive validity: sensitivity of .76 or .73 and specificity of .71 or .80. However, neither Briggs-Gowen et al. (2004) nor Gardner et al. (2013) obtained actual ASD diagnoses; they compared the scores to the CBCL/1.5–5 (Achenbach & Rescorla, 2000) and the M-CHAT (M-CHAT: Robins et al., 2001), respectively.

Modified Checklist for Autism in Toddlers (M-CHAT: Robins et al., 2001). The M-CHAT is a commonly used screener (Narzisi et al., 2013; Sunita & Bilszta, 2013). Sunita and Bilszta (2013) reported that the M-CHAT may be biased due to inclusion of early intervention population groups in the calculation of predictive values. Scarpa et al. (2013) found that show that participants with low maternal education and minority status were more likely to endorse items suggestive of ASD and concluded that there was poor internal inconsistency in these samples used (Thus, the generalizability of the M-CHAT needs more research.

Autism Observation Scale for Infants (AOSI, Zwaigenbaum et al., 2005). The AOSI is an 18-item clinician observation measuring tool designed specifically for infants at risk for ASD

between the ages of 6 and 18 months. Bryson & Zwaigenbaum (2014) revisited the AOSI to determine its feasibility as a screener for infants with no family history of ASD. The result suggested that AOSI is a reliable method for finding and observing ASD related behaviours in infants from 6 to 18 months old (Bryson & Zwaigenbaum, 2014). Nevertheless, the sensitivity of AOSI was unsatisfactory (Ben-Sasson & Carter, 2012; Bryson & Zwaigenbaum, 2014). The low sensitivity was mainly concentrated on groups of children with high verbal skills or mild symptoms of ASD, even though they were diagnosed with ASD later at the age of 3 years. Furthermore, AOSI also picked up symptoms similar to ASD on some children who were not later diagnosed with ASD.

ASD-Specific Second-Order Screeners Using Infants at Biological Risk

ASD-specific second-order screeners are designed specifically for infants at risk or were initially validated with this group. Given the fact that this population has a higher chance of developing ASD or a broader autism phenotype than the general population (Feldman et. al., 2012; Messinger et. al., 2013), it is important to have screener instruments that are validated with infants at risk.

First Year Inventory (FYI: Reznick et al., 2007) and ***First Year Inventory–Retrospective*** (FYI-R: Watson et al., 2007). The FYI and the FYI-R are parent-report measures designed for at risk infants at the age of 12 months. However, the FYI was not tested for any predictive values so further validation of the screener is needed. The FYI-R had acceptable predictive values, but because the parents completed the questionnaire retrospectively, prospective rates of sensitivity and specificity are unknown. Ben-Sasson and Carter (2012) conducted a study in Israel comparing the FYI with the AOSI (Zwaigenbaum et al., 2005) and the Mullen Scales of Early Learning (Mullen, 1995) with 17 at risk children and 38 low risk infants. The authors found that

the FYI showed similar detection results in the social-communication areas as the AOSI and was further verified by the language results of Mullen Scale. Ben-Sasson, Habib, and Tirosh (2014) found similar results to Ben-Sasson and Carter (2012) using the First Year Inventory–Lite, which is an abbreviated version of the original FYI (24 vs. 63 questions, respectively).

Parent Observation of Early Markers Scale **(**POEMS: Feldman et al., 2012, Appendix D**).** Feldman et al. (2012) identified a research gap: there was no valid early screener relying exclusively on parent report and including a range of ASD-specific symptoms and related behaviours in the first year of life. To fill the gap, Feldman and associates created the POEMS to efficiently identify ASD for later-born siblings of children with ASD (Feldman et al., 2012)**.** Consisting of 61 items, the POEMS is designed to be a simple and low-cost tool that can help parents to detect early signs of ASD and collateral behaviours often seen in young children with ASD, so as to access required services as early as possible. .In the preliminary study (Feldman et al., 2012), the families recruited had at least one biological child with an independent diagnosis of ASD, and a younger biological sibling. In total, 108 infants participated in the original study (including one set of identical twins and one set of non-identical twins). The POEMS had acceptable psychometric properties (internal consistency, test-retest reliability and construct validity) and predictive validity. By the end of the original prospective study, a total of nine children (6 males, 3 females) had received independent community diagnoses of ASD by 3 years of age. The POEMS differentiated the subsequently diagnosed from the undiagnosed at risk infants as early as 9 months of age. As diagnosis was determined at 3 years of age, it is possible that more children were diagnosed after this age. Hence, the follow-up study described in this thesis examined the POEMS predictive validity with children from the original sample who were or were not diagnosed with ASD both before and after age 3 years.

Purpose of Study and Hypothesis

This follow-up study further examined the POEMS predictive validity with children from the original sample who were or were not diagnosed with ASD before and after the age of 3 years. We included POEMS scores up to 36 months and added a group of at risk infants who lost their ASD diagnosis. We examined which POEMS items most differentiated the three groups at different ages. Our hypotheses were that the diagnosed with ASD group would have higher POEMS scores and more elevated items than the lost diagnosis and undiagnosed groups, and the lost diagnosis group would have higher POEMS scores and more elevated items than the undiagnosed group.

Method

Research Design

The research design consisted of a longitudinal, follow-up study of Feldman et al. (2012) that also included a between-group comparison of POEMS scores at different ages of at risk children who were or were not subsequently diagnosed with ASD, or who lost their diagnosis. The updated diagnostic status of the child was used to determine the predictive validity of the POEMS (i.e., sensitivity, specificity, and positive predictive value). We determined the ages at which significant differences in POEMS scores between the subsequently diagnosed, lost diagnosis and undiagnosed children emerged. We compared the most frequently elevated POEMS items in the ASD diagnosed and lost diagnosis groups to each other and to the undiagnosed children, across ages 9 to 36 months.

Participants

All the families who participated in the Feldman et al. (2012) study were contacted for the follow-up study if they had indicated they were willing to be contacted again (78 by email and 2

by phone). Of the 80 families contacted, eight did not return the questionnaires and 22 could not be reached. In sum, 54 at-risk infants from 50 families were invited to participate. Table 1 provides descriptive information of the participants who did (n = 54), and did not (n = 56) complete the follow-up information. One-way Analyses of Variance (ANOVAs) and Chi-squares conducted on 12 demographic variables and two POEMS scores - mean total score and elevated items (scores of $\geq$3) - revealed no statistically significant differences between the two groups on any variable. Therefore, we used the follow-up diagnostic data to update and re-analyze the POEMS results for the participants.

This follow-up study included 110 at-risk children: the same 108 infants from the Feldman et al. (2012) study, now children (the oldest child was 13 years old), plus two new infants who were born to two of the participating families after the Feldman et al. (2012) study analyses were completed. Figure 1 presents a flow-chart of how the diagnosed, lost diagnosis, and undiagnosed groups were formed from the original study. All diagnoses in diagnosed group were independent community diagnoses based on the DSM-IV-TR (American Psychiatric Association, 2000). Verbatim diagnoses in the diagnosed group were: Autism (7), Pervasive Developmental Disorder Not Otherwise Specified (3), Autistic Disorder (1), Asperger syndrome (1), and Autism Spectrum Disorder (1).

In summary, the follow-up study groups are diagnosed (n = 13), lost diagnosis (n = 5) and undiagnosed (n = 92). Table 2 provides descriptive information on the three groups. One-way ANOVA and Chi-squares analyses were conducted to determine if the three groups differed on the 10 demographic variables in Table 2. The results indicated that mother's age was significantly lower in the lost diagnosis group than the undiagnosed group, $p < .05$. None of the other variables were statistically significant between groups.

Measures and data collection procedures

Follow-up Questionnaire (FUPQ). This 7-item questionnaire was sent out by email to each family to complete. The goal of the questionnaire was to find out if there was an updated diagnosis for any of the nine children previously diagnosed and if any of the other children had received diagnoses. The questionnaire was designed to obtain information regarding the current diagnosis status of the at risk children, more specifically, whether or not they had an ASD or another disorder diagnosis; if yes, whether or not they still had the same or a different diagnosis, or if they had lost the ASD or another disorder diagnosis (see Appendix A).

Family Information Questionnaire (FIQ). The FIQ was sent out to each family to complete. The questionnaire contains census-type questions. There are two versions of the FIQ:

(1) The original FIQ: This is for families that did not complete the FIQ in the original study (see Appendix B). The original FIQ contains 34 questions in 5 sections: parent/family information, information about the child's biological mother and father, participant child information, and prenatal/birth history of the child.

(2) A FIQ update: This is for families that had completed the FIQ in the original study (see Appendix C). The FIQ update contains 21 questions in 4 sections: parent/family information, information about the child's biological mother and father, participant child information. All 21 questions are about situations that could possibly have changed since the completion of the last FIQ in the original study (e.g., number of children living in the home could have changed due to a later-born child).

Parent Observation of Early Markers Scale (POEMS, Feldman et al., 2012). Although no children received the POEMS (Appendix D) in the follow-up study, it is described here because all the children participating in this follow-up study had received at least one POEMS between

the ages of 1 and 36 months. There were a mean of 11.12 (*SD* = 6.61) POEMS administrations (range = 1 to 29) per child. The POEMS is a parent-report screener with 61 items, completed over the first 36 months of the child's life, preferably on a monthly basis. The parents knew the POEMS by the generic name, Parent Observation Checklist (POC). Each item is rated from 1 (not a problem) to 4 (severe problem), with ½ scores allowed. An elevated item is considered to be a rating of 3, 3.5 and 4. The items are organized by behaviours (e.g., eating, sleeping, social, communication, tolerance) and no subscales are used. If an item is too advanced for the age of the child, then the parents are asked to score NA. All NAs and nonscored items are converted to a score of 1, so that each child has a minimum score of 61 and a maximum score of 244. The Feldman et al. (2012) preliminary evaluation revealed a reasonable empirical cut-off score of 70 (differentiating subsequently diagnosed from undiagnosed children). Feldman et al. (2012) showed that the POEMS had acceptable psychometric properties and predictive validity. Overall sensitivity and specificity across the studied age ranges were .74 and .73, respectively. Positive predictive value (PPV) was low at .21, but may have been due to the "disproportionate number of non-diagnosed to subsequently diagnosed children" (Feldman et al., 2012, p.19).

Procedure

Initial contact. The original prospective families were contacted by email or phone with a request to participate in the follow-up study. Families that had requested no further contact at the end of the original prospective study were excluded. A second email or phone call requesting the families' participation was sent out to the families who did not respond to the initial request email within two weeks. If the families did not respond to the second request within one week, a phone call was made. The parents were asked to inform the researchers whether the parents wanted to participate or not. Therefore, nonresponse to the email did not necessarily mean that

they did not wish to participate (e.g., the email address was outdated; the emails went into their spam folders).

Completing the questionnaires. Those parents who agreed to participate were sent the FUPQ and the FIQ by email or postal mail, or received a phone interview. If the parents did not return the questionnaires within two weeks, they were sent a reminder email. After one more week, we phoned them if they still did not return the questionnaires. If they still did not return the questionnaires nor complete them over the phone, then we used their original data. Of the 50 families with 54 prospective children who participated the follow-up study, 21 families returned the FIQ and FUIQ by email; three returned them by mail; 20 completed the FIQ and FUIQ via phone interviews; and six completed the FUIQ via phone interviews.

Method of Data Analysis

The FUPQ results were used to update the number of children from the original POEMS prospective infant sample who had been diagnosed with ASD as well as create a new group that lost their ASD diagnoses. New POEMS sensitivity, specificity and positive predictive value (PPV) were calculated. Using inferential statistics (e.g., mixed design ANOVA with corrected pair-wise comparisons), we compared the mean POEMS total scores and elevated items (scores of 3, 3.5, 4, with 4 = max) of the diagnosed, lost diagnosis and undiagnosed groups across ages 1 to 36 months. We determined at what ages differences were first noted and how group differences changed over time. Finally, we examined which POEMS items from ages 9 to 36 months differentiated the three groups by looking at the percentage of children in each group who had elevated scores on each item. We reported the percentage of the children in the diagnosed and lost diagnosis groups with the most frequently reported elevated items in those

groups and compared those percentages to the percentages of children in the other two groups who also reported those items as elevated.

Results

Between-Group Comparisons

Figures 2 and 3 show that the diagnosed children had the highest mean total POEMS scores and elevated POEMS items (score ≥3), respectively, between 3 and 36 months followed by the lost diagnosed group and undiagnosed group. Overall means of total POEMS scores for the diagnosed, lost diagnosis, and undiagnosed groups were 89.0 (*SD* = 33.64), 73.70 (*SD* = 4.24), and 65.76 (*SD* = 8.17), respectively. The overall means of elevated items across ages for the diagnosed, lost diagnosis, and undiagnosed groups were 8.12 (*SD* =11.59), 2.0 (*SD* = 0.51), and 0.9 (*SD* = 1.98), respectively. In addition, the mean total POEMS scores and number of elevated items in the diagnosed groups increased as the children became older.

A mixed model of ANOVA using type III sums of squares for children with total score data from 9, 12, 18, 24 and 36 months revealed that the POEMS total scores differed between groups F (2, 77) = 13.61, $p <$ .001, partial eta-squared (η_p^2) = .026, and group X age interaction was significant, F (8, 308) = 3.36, $p <$ .001, η_p^2 = .080. To control the Type I error, *post hoc* corrected comparisons were conducted using the Tukey Honestly Significant Difference (HSD) test; the results showed that the diagnosed group (*M* = 89, *SD* = 33.65) had significantly higher total scores, $p < .05$, than the undiagnosed group (*M* = 65.76, *SD* = 8.18). The lost diagnosis group (*M* = 73.70, *SD* = 4.23) did not differ significantly from the diagnosed and undiagnosed groups. The groups differed on the number of elevated items, F (2, 77) = 15.17, $p <$ .001, η_p^2 = .28, and group X age was significant, F (8, 308) = 3.08, $p <$ .001, η_p^2 = .074. *Post hoc* comparisons using the Tukey HSD test showed that the diagnosed group (*M* = 8.12, *SD* = 11.59)

had significantly more elevated items than the undiagnosed group (M = .90, SD = 1.98), but the lost diagnosis group (M = 2.00, SD = .51) did not. The latter group also did not differ from the undiagnosed group. Repeated measures analyses revealed a significant age effect as the children aged on total POEMS scores, F (4, 308) = 4.40, $p <$ .005, η_p^2= .054, but not significant for elevated items, F (4, 308) = 2.28, p = .060, η_p^2 = .032. The *Post hoc* Tukey test on repeated measures showed that the diagnosed group had significantly higher, $p < .05$, total scores and elevated items than the undiagnosed group at 9, 12, 18, 24, and 36 months of age. In addition, the Tukey test showed that the diagnosed group had significantly higher total scores than the lost diagnosis group at 18 months of age, and more elevated items at age 18, 24, and 36 months, $p <$ .05. The lost diagnosis group was not significantly different from the undiagnosed group on POEMS total scores and elevated items at any age.

Table 3 shows the highest percentage (≥ 30%) of POEMS elevated items in the diagnosed groups compared to the lost diagnosis and undiagnosed groups at 9, 12, 18, 24 and 36 months of age. Problems with imitation, verbal communication, pointing in response to a question, tolerance for waiting and acceptance of food most differentiated the at-risk infants who were eventually diagnosed from those who had not been diagnosed by age 13 years. As seen in Table 3, the POEMS elevated items of the diagnosed group followed a developmental progression with the diagnosed and the lost diagnosis groups having higher elevations for POEMS items at all ages compared to the undiagnosed group that had few elevated items at any ages (its highest percentage of an elevated item was 46% for appetite at 24 months).

Table 4 shows the highest percentage (≥ 30%) of POEMS elevated items in the lost diagnosis group compared to the diagnosed and undiagnosed groups at 9, 12, 18, 24 and 36 months of age. The percentages may be overestimates given the small sample size of the lost

diagnosis group. Similar to the diagnosed group, the lost diagnosis group also had a developmental progression on the POEMS elevated items. Pointing to shared interest, pointing to request, and pointing to response to questions could be challenges for children in the lost diagnosis group.

Sensitivity, Specificity and Positive Predictive Value

The lost diagnosis group was not included in calculating predictive values because its scores were between those of the diagnosed and undiagnosed groups (see Figures 1 and 2) and its members' diagnostic status is ambiguous at different points in the study. This study calculated the predictive values using the same cut-off score as the original study, 70. Sensitivity, specificity, and PPV were .69, .84, and .38, respectively. We re-calculated the predictive values using a new cut-off score, 65, to increase the sensitivity since that is important for a screening instrument. The results showed that 65 might be a more sensitive cut-off score: the sensitivity increased to .85. However, lowering the cut-off score decreased the specificity and PPV to .64 and .25, respectively. However, these values may be hampered by the very small sample size of diagnosed children.

Discussion

In this longitudinal follow-up study, the data from the infants from the original Feldman et al. (2012) POEMS study were combined with the follow-up data. The goal was to further validate the POEMS and compare the differences among three groups (diagnosed, lost diagnosis and undiagnosed) of children up to 13 years old with respect to their earlier POEMS total scores and elevated items. These analyses show that the POEMS has potential as a second-degree ASD screener for children at risk. The POEMS scores of the three groups (subsequently diagnosed, lost ASD diagnosis and undiagnosed) aligned as expected, with the lost diagnosis group scores

falling between those of the other two groups. This ordering of the three groups' means also suggests that although the parents had older children with ASD, they appeared to accurately report the problems of the younger siblings and were not uniformly biased to provide high scores. Given the small sample size of the lost diagnosis group, we could not confirm our hypothesis of overall significant differences between this group and the other two groups on POEMS total scores and elevated items. Nonetheless, as would be expected, pair-wise comparisons revealed that the lost diagnosis group started having significantly fewer elevated items than the diagnosed group starting at 18 months of age. The group X age interaction of POEMS total scores indicated that the POEMS scores diverged as the children aged, which is consistent with other research (Lemcke et al., 2013). As in the original Feldman et al. (2012) study with basically the same sample of at-risk children (but with differences in which children were eventually diagnosed), significant differences in POEMS total scores and elevated items between the diagnosed and the undiagnosed at risk children emerged as early as 9 months of age. Previous studies that had detected early signs of ASD prior to 12 months primarily were detailed retrospective analyses of home movies by ASD researchers (Barbaro & Dissanayake, 2009; Yirmiya, & Charman, 2010). The results of this study indicate that the POEMS may be an effective screener for at risk infants up to 36 months of age, and may be sensitive in detecting differences in at risk infants who remain diagnosed versus those who will eventually lose their ASD diagnosis (although a larger sample is needed).

The POEMS elevated items most frequently reported by the parents of diagnosed children were social and communication problems. This finding has also been seen in other at-risk infant studies (Curtin & Vouloumanos, 2013; Green et. al., 2013; Hudry et. al., 2014; Jones et. al., 2014). The concerned areas included imitation, verbal communication, pointing in response to a

question, and interests in face. Some other POEMS items frequently reported did not belong to the two core domains of ASD such as waiting and appetite. Even though such behaviours are not core characteristics of ASD, they are common challenges in young children with ASD (Campillo et. al., 2014; Kral et. al., 2013), and may be early markers in at risk infants. Similar to the diagnosed group, the lost diagnosis group had many frequently reported items falling in the section of social and communication deficits. The fact that the early markers reported by the parents on the POEMS were consistent with findings from previously published studies using professional observations and testing (Gardner et al., 2013; Ghuman et al., 2011) provides further evidence that the parents can be accurate prospective reporters of their children's development. Consistently receiving elevated scores on one or more POEMS items could be used as an indication that such at-risk infants should begin receiving interventions targeting those items in order to help reduce possible symptoms of a broadband autism phenotype.

For parents with at risk infants, the POEMS is a low-cost and easy-to-use screener tool to monitor the infants' development. This is particularly helpful for families with limited resources in funding and access to professionals (e.g., rural families). Research shows that families with children with ASD earn less in the US and Canada, and the families are less likely to have both parents working usually because one parent (usually the mother) stays home to care for the affected child (Boyles, 2012; Cidav, Marcus, & Mandell, 2012; Feldman et al., 2014).

There are some limitations to this study. First, the sample of 13 diagnosed children is still relatively small when compared to other at risk infants or screener validation studies (Gardner et al., 2013; Narzisi et al., 2013; Nygren et al., 2012) and thus interferes with the strength of the predictive values. Second, the return rate on the follow-up questionnaire represents only about 50% of the original Feldman et al. (2012) study sample, therefore, the assumption that the

diagnostic status of the non-participating families remaining the same for all noncontacted children may not be correct. Perhaps, providing a monetary honorarium would increase follow-up participation rates. Third, we did not obtain information on ethnicity and first language other than English, both of which may affect participation rates and POEMS scoring. ASD prevalence may be different among ethnicities (Jo et al., 2015; Pedersen et al., 2012) and minority group status may positively skew scoring on an ASD screener (Scarpa et al., 2013). Fourth, although the results are intriguing and in the expected direction, the sample of five lost diagnosis children is too small to allow firm conclusions to be drawn about how the POEMS differentiates this group from the other two groups. Theoretically, a larger sample would result in increased numbers in each group and improve the overall strength of the findings as well as provide more participants in the lost diagnosis group. A larger sample could permit further analyses to more accurately determine which items differentiate the diagnosed group from the lost diagnosis group at younger ages. We also do not know why children in the lost diagnosis group lost their diagnoses as we did not have information on interventions or other events that may have led to changes in diagnosis.

Conclusion

This study provides further evidence that the POEMS is an effective, low-cost, second-degree ASD screener for infants having older siblings with ASD. The POEMS differentiated at risk infants subsequently diagnosed with ASD and undiagnosed with ASD up to 13 years of age. At risk children who lose their ASD diagnosis traditionally have received little or no attention in research studies. The finding that the POEMS scores of the lost ASD diagnosis group fell between those of the diagnosed and undiagnosed groups, with significantly lower scores than the diagnosed group starting at 18 months is intriguing, but a larger sample is needed to determine

the strength of this result. Further POEMS studies with larger samples of at-risk and general population children may increase the strength of the results overall and to allow further analyses of the lost diagnosis group.. An emerging research area is pre-diagnostic interventions for infants showing early signs of ASD (e.g., Green et al., 2015; Rogers et al., 2014) and the POEMS may be useful in identifying and tracking children in need of targeted interventions.

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Table 1

Characteristics of Participants in the original study who did and not complete follow-up information

Variables	Completed Follow-up Information	Did Not Complete Follow-up Information
Number of children	54	56
Percentage male infants	63.0%	70.9%
Mean age (months) of affected siblings start of study (SD)	127.82(16.48)	128.04(16.74)
Percentage of affected siblings who were male	100%	44.44%
Percentage mothers at start of study (years) (SD)	46.43(4.73)	45.54(4.13)
Percentage mothers with at least a college/university degree	88.6%	81.5%
Percentage mothers employed other than or in addition to homemaker	72%	75%
Mean age of fathers at start of study (years) (SD)	47.92(5.35)	47.07(4.87)
Percentage fathers with at least a college/university degree	39.7%	54.5%
Percentage fathers employed other than	98.10%	93.90%

or in addition to homemaker		
Range of reported annual family income (lowest - highest income range)	$10k to >100k	$20k to >100k
Percentage of two parent families	92.60%	90.40%
Mean POEMS scores (SD)	68.55(10.02)	69.20(19.37)
Mean number of elevated items (SD)	1.38(2.66)	2.22(6.28)

Table 2

Characteristics of Children and Families in Diagnosed (n = 13), Lost Diagnosis (n = 5) and Undiagnosed (n = 92) Groups

Variables	Diagnosed	Lost Diagnosed	Undiagnosed
Mean age of infants at start of study (months)	138.11	138.9	140.88
(*SD*)	(20.04)	(12.85)	(15.97)
Percentage male infants	61.50%	100.0%	66.7%
Mean age of mothers at start of study (years) (SD)	44.51(5.13)	40.37(4.85)*	45.32(4.21)
Percentage mothers with at least a college/university degree	81.8%	100%	85.5%
Percentage mothers employed other than or in addition to homemaker	77.80%	80.00%	71.70%
Mean age of fathers at start of study (years) (SD)	45.99(6.48)	49.86(9.25)	47.55(4.62)
Percentage fathers with at least a college/university degree	63.7%	100.00%	70.9%
Percentage fathers employed other than or in addition to homemaker	100.0%	100.00%	95.60%
Range of annual family income (lowest—highest income range)	$30k to > 100k	$30k to > 100k	$10k to >100K
Percentage of two-parent families	100%	100.00%	89.70%

*Lost diagnosis < undiagnosed, $p < .05$

Table 3

The Most Frequently Reported Elevated POEMS Items in the Diagnosed group by age (months) compared to the lost diagnosis and undiagnosed groups

Age (Months)	Elevated item on POEMS	% diagnosed participants	% lost diagnosed participants	% undiagnosed participants
9	Milk/formula tolerance	44 (n = 9)	60 (n = 5)	11 (n = 53)
	Acceptance of new food	33	0	4
	Response to name	33	0	4
	Agility in Movement	33	0	2
	Waiting	33	20	6
12	Acceptance of new food	45 (n = 11)	0 (n = 5)	8 (n = 71)
	Milk/formula tolerance	36	60	11
	Appetite	36	0	10
	Imitates actions	36	0	7
	Waiting	36	20	10
18	Imitates actions	62 (n = 13)	40 (n = 5)	9 (n = 85)
	Waiting	62	20	12
	Communicates with words	62	40	16
	Acceptance of new food	54	0	12
	Appetite	46	0	14
	Building tower	46	0	9
	Pointing to share interest	46	100	12
	Coordinates point and gaze	46	80	11
	Points in response to questions	46	60	9
	Waves bye-bye	46	60	6
	Coordinate gestures with communication	46	0	6
	Conventional use of words	46	0	9
	Milk/formula tolerance	38	60	18
	Laughing	38	0	1
	Attachment to parents	38	0	5
	Shifts attention to person	38	20	1
	Imitates sounds or words	38	60	22
	Pretend play	38	60	9

	Pointing to request	38	80	12
	Follows adult point with gaze	38	60	8
	Follows simple direction	38	60	9
	Bring toy to share attention	38	0	8
	Waiting	38	20	6
	Sleep duration at night	30	20	16
	Response to name	30	40	5
	Interest faces	30	20	6
	Object permanence	30	60	8
	Agility in movement	30	0	2
	Attention Span	30	0	2
	Interest in birthdays/presents	30	0	2
24	Waiting	69 (n = 13)	20 (n = 5)	2 (n = 89)
	Communicates with words	69	40	1
	Imitates actions	62	60	19
	Acceptance of new food	54	0	2
	Pointing to share interest	54	100	1
	Coordinates point and gaze	54	80	0
	Pints in response to questions	54	80	2
	Bring toy to request	54	80	6
	Conventional use of words	54	40	0
	Appetite	46	0	46
	Imitates sounds or words	46	80	1
	Pointing to request	46	80	6
	Follows adult point with gaze	46	60	1
	Coordinate gestures with communication	46	0	0
	Sleep duration at night	38	20	0
	Milk/formula tolerance	38	60	16
	Laughing	38	0	10
	Attachment to parents	38	0	3
	Shifts attention to person	38	20	0
	Pretend play	38	80	0
	Follows simple direction	38	60	4
	Bring toy to share attention	38	0	2
	Waiting	38	20	1
	Nap time	30	0	15

	Response to name	30	40	3
	Interest faces	30	20	7
	Object permanence	30	60	3
	Agility in movement	30	0	4
	Attention Span	30	0	13
	Interest in birthdays/presents	30	0	1
36	Waiting	69 (n = 13)	20 (n = 5)	14 (n = 92)
	Communicates with words	69	60	20
	Imitates actions	62	80	9
	Acceptance of new food	54	20	16
	Imitation sounds or words	54	100	22
	Pointing to share interest	54	100	11
	Coordinates point and gaze	54	80	10
	Points in response to questions	54	80	10
	Follows adult point with gaze	54	60	10
	Waves bye-bye	54	80	5
	Coordinate gestures with communication	54	20	8
	Conventional use of words	54	60	14
	Milk/formula tolerance	46	60	16
	Appetite	46	20	18
	Shifts attention to person	46	20	3
	Building tower	46	0	10
	Pointing to request	46	80	12
	Sleep duration at night	38	20	15
	Laughing	38	0	2
	Attachment to parents	38	0	5
	Pretend play	38	80	10
	Follows simple direction	38	60	9
	Bring toy to request	38	0	8
	Bring toy to share attention	38	20	8
	Nap time	30	0	13
	Mood	30	0	9
	Response to name	30	40	5
	Interest faces	30	20	10
	Object permanence	30	60	8
	Agility in movement	30	0	3
	Attention Span	30	0	2
	Interest in birthdays/presents	30	0	2

Table 4

The Most Frequently Reported Elevated POEMS Items in the lost diagnosis group by age (months) compared to the diagnosed and undiagnosed groups

Age (Months)	Elevated item on POEMS	% lost diagnosed participants	% diagnosed participants	% undiagnosed participants
9	Milk/formula tolerance	60 (*n* = 5)	44 (*n* = 9)	11 (*n* = 53)
	Anticipation to being picked up	40	22	4
	Pointing to request	40	0	2
	Pointing to share interest	40	11	2
	Coordinates point and gaze	40	0	0
12	Milk/formula tolerance	60 (*n* = 5)	36 (*n* = 11)	11 (*n* = 71)
	Anticipation to being picked up	40	18	1
	Response to name	40	27	6
	Pointing to request	40	18	11
	Pointing to share interest	40	27	11
	Coordinates point and gaze	40	27	10
18	Pointing to share interest	100 (*n* = 5)	46 (*n* = 13)	12 (*n* = 85)
	Pointing to request	80	38	12
	Coordinates point and gaze	80	46	11
	Milk/formula tolerance	60	38	18
	Anticipation to being picked up	60	23	6
	Object permanence	60	31	8
	Imitates sounds or words	60	38	22
	Pretend play	60	38	9
	Pints in response to questions	60	46	9
	Follows adult point with gaze	60	38	8
	Follows simple direction	60	38	9
	Bring toy to request	60	46	6
	Response to name	40	31	5
	Imitates actions	40	62	9
	Communicates with words	40	62	16
24	Pointing to share interest	100 (*n* = 5)	54 (*n* = 13)	1 (*n* = 89)

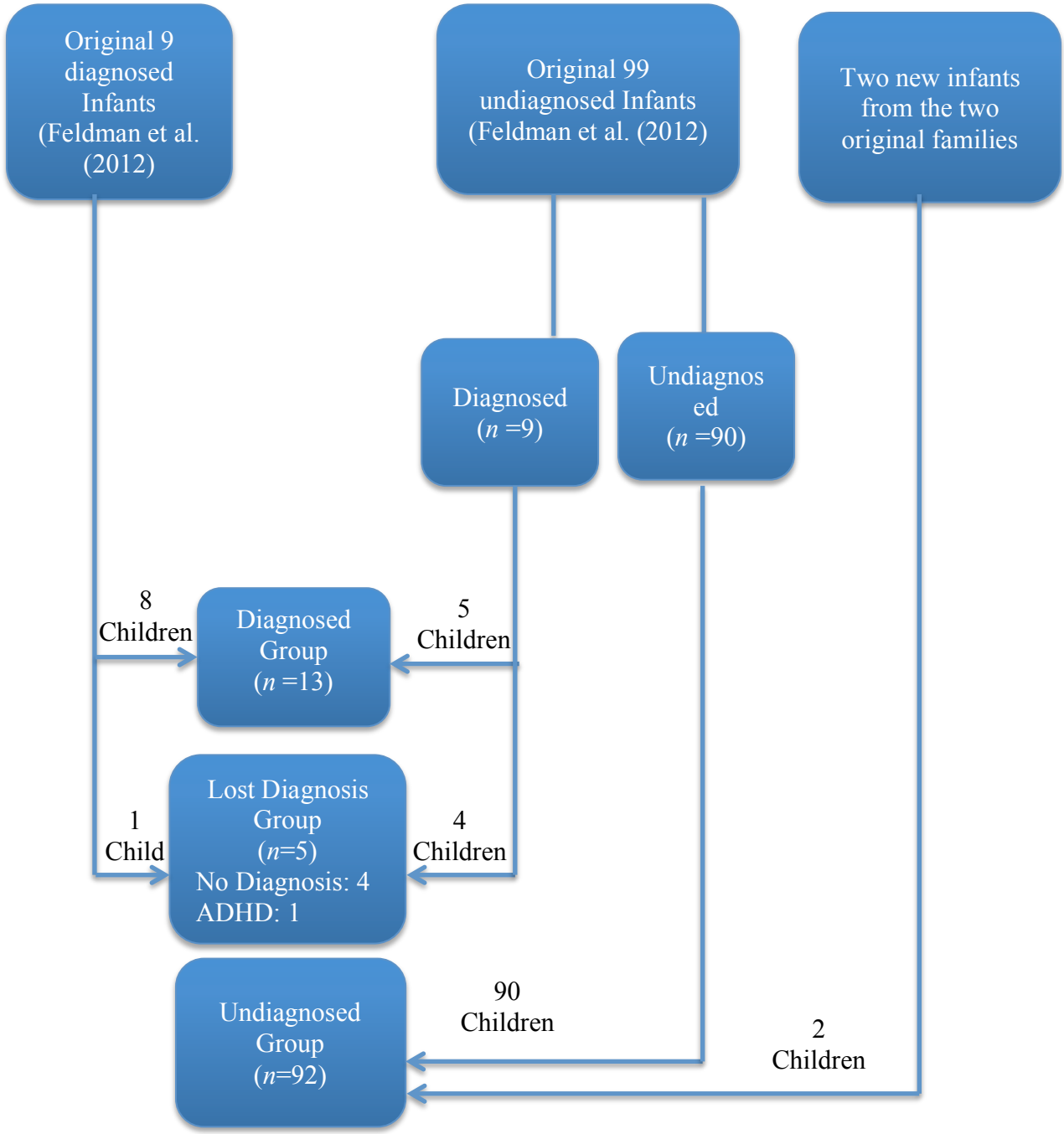
	Imitates sounds or words	80	46	1
	Pretend play	80	38	0
	Pointing to request	80	46	6
	Coordinates point and gaze	80	54	0
	Pints in response to questions	80	54	2
	Bring toy to request	80	54	6
	Milk/formula tolerance	60	38	16
	Anticipation to being picked up	60	23	4
	Object permanence	60	31	3
	Imitates actions	60	62	19
	Follows adult point with gaze	60	46	1
	Follows simple direction	60	38	4
	Response to name	40	31	3
	Communicates with words	40	69	1
	Conventional use of words	40	54	0
36	Imitates sounds or words	100 (n = 5)	54 (n = 13)	22(n = 92)
	Pointing to share interest	100	54	11
	Imitates actions	80	62	9
	Pretend play	80	38	10
	Pointing to request	80	46	12
	Coordinates point and gaze	80	54	10
	Points in response to questions	80	54	10
	Wave Good-bye	80	54	5
	Milk/formula tolerance	60	46	16
	Anticipation to being picked up	60	23	5
	Object permanence	60	31	8
	Follows adult point with gaze	60	54	10
	Follows simple direction	60	38	9
	Communicates with words	60	69	20
	Conventional use of words	60	54	14
	Response to name	40	31	5

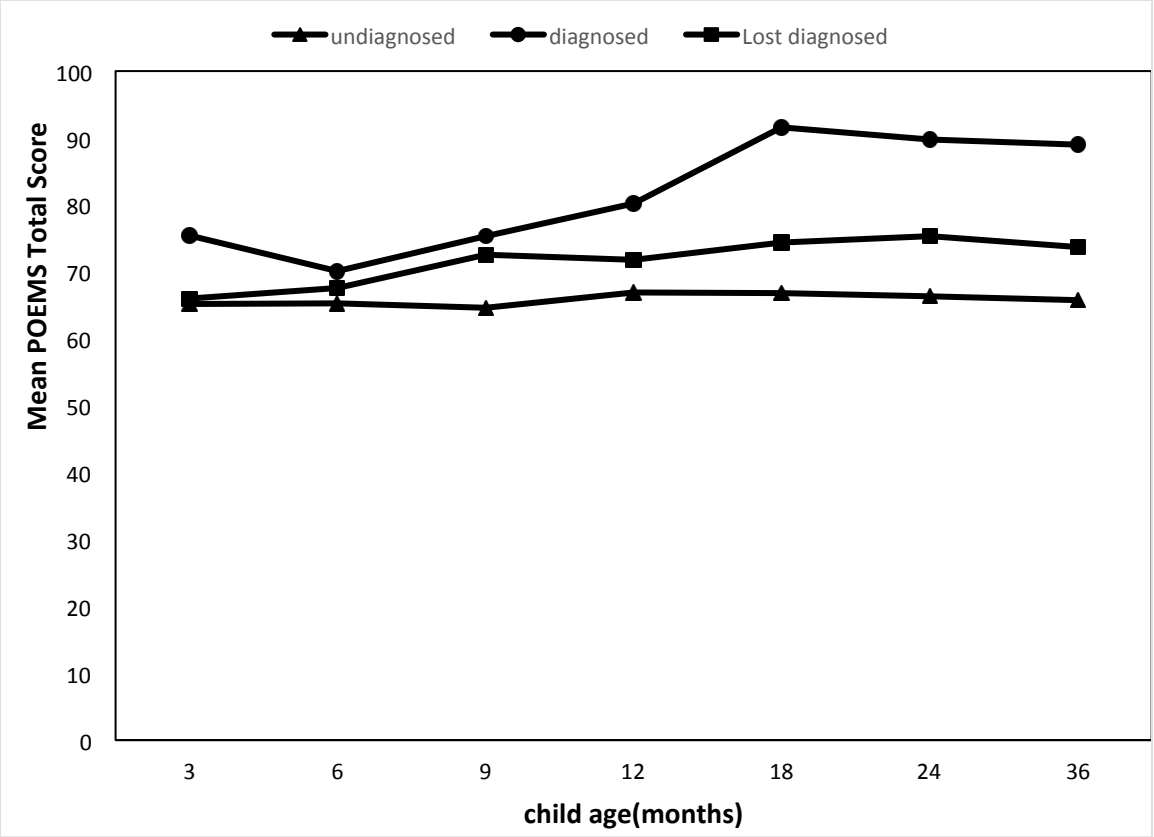
Figure Captions

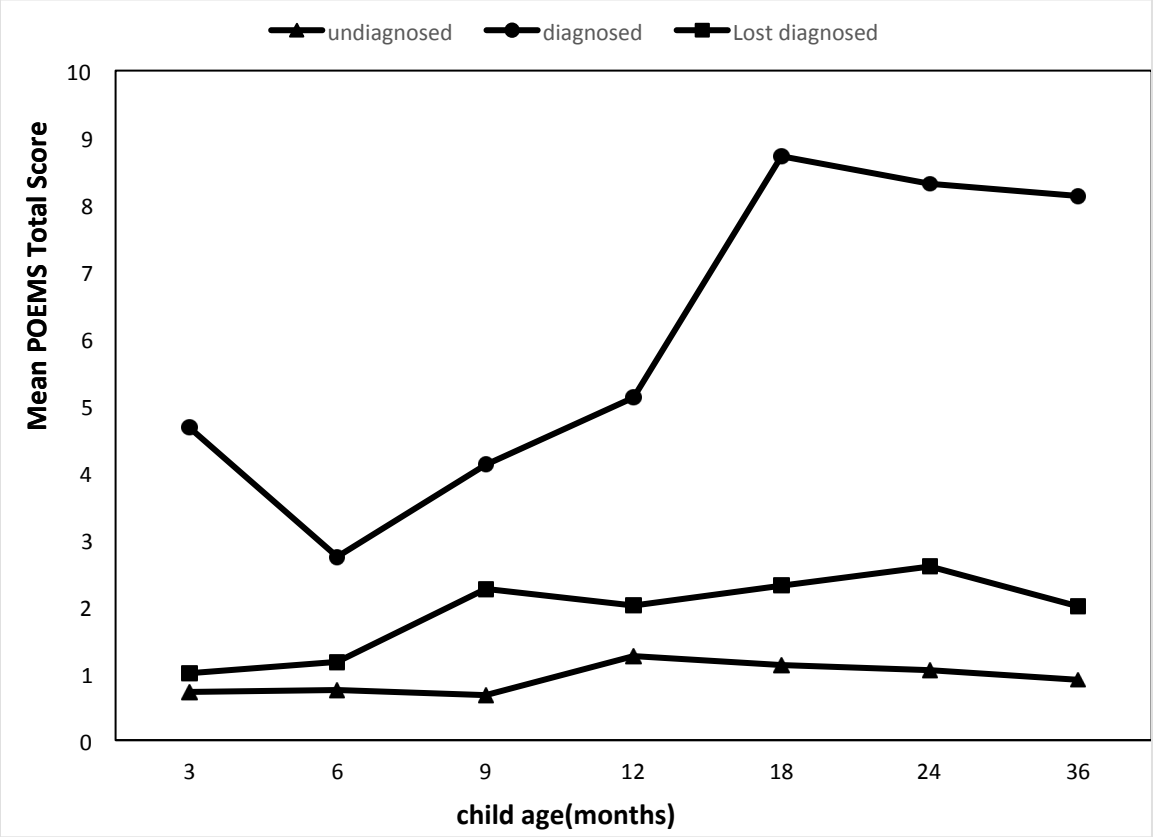
Figure 1. Diagnosed, lost diagnosis, and undiagnosed groups flow chart.

Figure 2. Mean total POEMS scores at 3 months (*n's* = 3 diagnosed, 1 lost diagnosis, 17 undiagnosed); 6 months (*n's* = 7 diagnosed, 4 lost diagnosis, 40 undiagnosed); 9 months (*n's* = 9 diagnosed, 5 lost diagnosis, 53 undiagnosed); 12 months (*n's* = 11 diagnosed, 5 lost diagnosis, 71 undiagnosed); 18 months (*n's* = 13 diagnosed, 5 lost diagnosis, 85 undiagnosed); 24 months (*n's* = 13 diagnosed, 5 lost diagnosis, 89 undiagnosed); and 36 months (*n's* = 13 diagnosed, 5 lost diagnosis, 92 undiagnosed) of age of the diagnosed, lost diagnosis and undiagnosed groups.

Figure 3. Mean POEMS elevated items (scores of 3, 3.5 or 4) at 3 months (*n's* = 3 diagnosed, 1 lost diagnosis, 17 undiagnosed); 6 months (*n's* = 7 diagnosed, 4 lost diagnosis, 40 undiagnosed); 9 months (*n's* = 9 diagnosed, 5 lost diagnosis, 53 undiagnosed); 12 months (*n's* = 11 diagnosed, 5 lost diagnosis, 71 undiagnosed); 18 months (*n's* = 13 diagnosed, 5 lost diagnosis, 85 undiagnosed); 24 months (*n's* = 13 diagnosed, 5 lost diagnosis, 89 undiagnosed); and 36 months (*n's* = 13 diagnosed, 5 lost diagnosis, 92 undiagnosed) of age of the diagnosed, lost diagnosis and undiagnosed groups.


Original 9 diagnosed Infants (Feldman et al. (2012)
Original 99 undiagnosed Infants (Feldman et al. (2012)
Two new infants from the two original families
Diagnosed (n =9)
Undiagnosed (n =90)
8 Children
Diagnosed Group (n =13)
5 Children
1 Child
Lost Diagnosis Group (n=5) No Diagnosis: 4 ADHD: 1
4 Children
Undiagnosed Group (n=92)
90 Children
2 Children


undiagnosed
diagnosed
Lost diagnosed
Mean POEMS Total Score
100
90
80
70
60
50
40
30
20
10
0
3
6
9
12
18
24
36
child age(months)


undiagnosed
diagnosed
Lost diagnosed
Mean POEMS Total Score
10
9
8
7
6
5
4
3
2
1
0
3
6
9
12
18
24
36
child age(months)

Appendix A

Follow-up Questionnaire

Name of Child (who participated in ASD-CARC Prospective Study):

First Name: _____ Last Name: _____

Child Date-of-Birth (mm-dd-yy): _____

Name of Person Completing this Form: _____

Relationship to Child: _____

Date: _____

The questions below pertain to your child who participated in the Queen's University ASD-CARC Prospective Study a few years ago. We are interested in an update about your child. Please answer the following questions:

1. Has your child ever been diagnosed with Autism Spectrum Disorder (ASD)? _____

   If your child has never been diagnosed with ASD, please go to Question 6

   If your child has been diagnosed with ASD at any time, please answer Questions 2-5 and 8

2. If your child has ever received an ASD diagnosis, please indicate which one (bold if an electronic version; circle if a hard-copy):

   ASD Autism Autistic Disorder Asperger Syndrome

   High Functioning Autism Pervasive Developmental Disorder Not Otherwise Specified

   Other ASD diagnosis (specify): _____

3. Does your child currently have this same ASD diagnosis? _____

   If no, when did he/she lose the diagnosis or the diagnosis changed?

   _____

   If the diagnosis changed, what did it change to? _____

   Comments:_____

4. Has your child also ever been diagnosed with another disorder in addition to ASD? Please indicate all that apply (bold if an electronic version; circle if a hard-copy): ADHD ADD Language Disorder or delay Anxiety Disorder OCD Learning Disability Epilepsy/Seizure Disorder Intellectual Disability Developmental Delay Other (specify):_____
5. Does your child currently have this same diagnosis(es)? _____ If no, when did he/she lose the diagnosis(es)?_____ Comments:_____
6. If your child has **never** been diagnosed with ASD, but he/she has been diagnosed with another disorder, please indicate all that apply: ADHD ADD Language Disorder/Delay Anxiety Disorder OCD Learning Disability Epilepsy/Seizure Disorder Intellectual Disability Developmental Delay Other (specify):_____
7. Does your child currently have this same diagnosis(es)? _____ If no, when did he/she lose the diagnosis(es)?_____ Comments:_____
8. If your child has received an ASD diagnosis and/or another diagnosis, please complete the information below to the best of your knowledge. Please refer to the diagnostic report if you have it, or alternatively, you can scan and email the report to _____ or fax to _____. Date of report:_____ Age of child at time of diagnosis (year, month): _____ Name of professional who diagnosed your child: _____ Credentials of professional who diagnosed:

Family Physician Pediatrician Psychiatrist Psychologist

Other (specify): _____

Affiliation of professional who diagnosed: _____

Address of professional who diagnosed:_____

Tests used to diagnose (if known): _____

Thank you for taking the time to complete this questionnaire!

Appendix B

FAMILY INFORMATION QUESTIONNAIRE (FULL)

1. Date (month-day-year) _____
2. Relationship to the child in the study _____
3. Participant child's name (first, last) _____
4. Participant child's date of birth (month-day-year) _____

PARENT/FAMILY INFORMATION

5. Number of all children and adolescents (up to age 18 years) living in the home: _____

   Age: _____ Relationship to participant child _____

   Age: _____ Relationship to participant child _____

   Age: _____ Relationship to participant child _____

   Age: _____ Relationship to participant child _____

   Age: _____ Relationship to participant child _____

6. Number of all adults (19 years and over) living in the home: _____
7. Present marital status of parents (Check ONE):
   Married Living together Separated Divorced Widowed
8. Total family income (Check ONE):

Less than $10,000	*$10,000-$20,000*	$20,000-$30,000	$30,000-$40,000
$40,000-$50,000	$50,000-$60,000	$60,000-$70,000	$70,000-$80,000
$80,000-$90,000	*$90,000-$100,000*	more than $100,000	

INFORMATION ABOUT CHILD'S BIOLOGICAL MOTHER

9. Mother's date of birth (month-day-year): _____
10. Highest education obtained by mother (Check ONE):

    None High School Trade diploma College University Graduate/Professional
11. Mother received special education services when in school (Check ONE):

    No Yes (specify): _____
12. Current occupation of mother: _____
13. Mother works (Check ONE):

    Full-time Part-time Homemaker Other _____
14. In general, how is mother's health? (Check ONE)

    Excellent Very good Good Fair Poor Don't know

INFORMATION ABOUT CHILD'S BIOLOGICAL FATHER

15. Father's date of birth (month-day-year): _____

16. Highest education obtained by father (Check ONE):

None High School Trade diploma College University Graduate/Professional

17. Father received special education services when in school (Check ONE):

No Yes (specify): _____

18. Current occupation of father: _____

19. Father works (Check ONE):

Full-time Part-time Homemaker Other _____

20. In general, how is father's health? (Check ONE)

Excellent Very good Good Fair Poor Don't know

PARTICIPANT CHILD INFORMATION (replicate if more than 1 child)

21. Child's initials _____

22. Child's sex (Check ONE):

- o Male
- o Female

23. Child's birth order (Specify number): _____

24. Child's siblings (Specify numbers for each category)

a. Younger Brothers _____

b. Younger Sisters _____

c. Older Brothers _____

d. Older Sisters _____

25. In general, how is your child's health? (Check ONE):

Excellent Very good Good Fair Poor Don't know

If poor, please explain

_____

_____

_____

_____

_____

26. In general, how is your child's development? (Check ONE):

Excellent Very good Good Fair Poor Don't know

If poor, please explain _____

27. In general, how is your child's behaviour? (Check ONE):

Excellent Very good Good Fair Poor Don't know

If poor, please explain _____

28. Does the participant child have any chronic medical conditions such as epilepsy, diabetes, cancer, hearing impairment, allergies or asthma?

Yes No

If Yes, please specify _____

29. Does the child have any syndrome, developmental or behavioural diagnosis (e.g., Down syndrome, cerebral palsy, Global Developmental Delay, autism, ADHD)?

    Yes No
    If Yes, please list _____
30. Is the participant child taking any medications currently?

Yes No
If Yes, please list _____

PRENATAL AND BIRTH HISTORY OF PARTICIPANT CHILD

31. Length of pregnancy: full-term _____ Premature? (how many weeks): _____
32. Any medical complications during **pregnancy**? (Check ONE)

    No Yes (Please specify): _____
33. Any medical complications during **birth**? (Check ONE)

    No Yes (Please specify): _____
34. Birth weight: _____ (indicate grams or pounds)

Appendix C

FAMILY INFORMATION QUESTIONNAIRE (Abbreviated)

Name of Child (who participated in ASD-CARC Prospective Study):

First Name: _____ Last Name: _____

Child Date-of-Birth (mm-dd-yy): _____

Name of Person Completing this Form: _____

Relationship to Child: _____

Date: _____

The questions below pertain to a Parents Observation Checklist study you and your child(ren) participated in the Queen's University Prospective Study a few years ago. We are interested in an update about your family.

Please provide updated information, where relevant, to the questions below. If there has been no change since the last time you completed the Family Information Questionnaire, please bold (on electronic copy) or circle (on hard copy) the word "Same" for that question. Thank you.

PARENT/FAMILY INFORMATION

35. Number of all children and adolescents (up to age 18 years) living in the home: _____

    Same

    Age: _____ Relationship to participant child _____

    Age: _____ Relationship to participant child _____

    Age: _____ Relationship to participant child _____

    Age: _____ Relationship to participant child _____

    Age: _____ Relationship to participant child _____

36. Number of all adults (19 years and over) living in the home: _____

    Same

37. Present marital status of parents (Check ONE):

    Same

    Married *Living together* *Separated* *Divorced* *Widowed*

38. Total family income (Check ONE):

    Same

Less than $10,000	*$10,000-$20,000*	$20,000-$30,000	$30,000-$40,000
$40,000-$50,000	$50,000-$60,000	$60,000-$70,000	$70,000-$80,000
$80,000-$90,000	*$90,000-$100,000*	more than $100,000	

INFORMATION ABOUT CHILD'S BIOLOGICAL MOTHER

39. Highest education obtained by mother (Check ONE):

    Same

    None High School Trade diploma College University Graduate/Professional

40. Mother received special education services when in school (Check ONE):

    Same

    No Yes (specify): _____

41. Current occupation of mother: _____

    Same

42. Mother works (Check ONE):

    Same

    No Full-time Part-time Homemaker

43. In general, how is mother's health? (Check ONE)

    Same

    Excellent Very good Good Fair Poor Don't know

INFORMATION ABOUT CHILD'S BIOLOGICAL FATHER

44. Highest education obtained by father (Check ONE):

    Same

    None High School Trade diploma College University Graduate/Professional

45. Father received special education services when in school (Check ONE):

    Same

    No Yes (specify): _____

46. Current occupation of father: _____

    Same

47. Father works (Check ONE):

    Same

    No Full-time Part-time Homemaker

48. In general, how is father's health? (Check ONE)

    Same

    Excellent Very good Good Fair Poor Don't know

PARTICIPANT CHILD INFORMATION (replicate if more than 1 child)

49. Child's siblings (Specify numbers for each category)

Same

a. Younger Brothers _____
b. Younger Sisters _____
c. Older Brothers _____
d. Older Sisters _____

50. In general, how is your child's health? (Check ONE):

Same

Excellent Very good Good Fair Poor Don't know

If poor, please explain _____

51. In general, how is your child's development? (Check ONE):

Same

Excellent Very good Good Fair Poor Don't know

If poor, please explain _____

52. In general, how is your child's behaviour? (Check ONE):

Same

Excellent Very good Good Fair Poor Don't know

If poor, please explain _____

53. Does the participant child have any chronic medical conditions such as epilepsy, diabetes, cancer, hearing impairment, allergies or asthma?

Same

Yes No

If Yes, please list _____

54. Does the child have any syndrome, developmental or behavioural diagnosis (e.g., Down syndrome, cerebral palsy, Global Developmental Delay, autism, ADHD)?

Same

Yes No

If Yes, please list _____

55. Is the participant child taking any medications currently?

Same

Yes No

If Yes, please list _____

Thank you for taking the time to complete this questionnaire!

Appendix D

Parent Observation Checklist

PARENT INSTRUCTIONS:

- *This checklist is to be completed on your infant every month, if possible (minimum every 3 months)*
- *The following infant/toddler behaviors are grouped together by topic and are NOT developmentally sequenced.*
- *Over the past week, please indicate with a score from 1-4 whether the child has no difficulty (score* 1*) to* severe problem *(score 4) for each item. If you are unsure about how to score an item, you can test it out with your infant/toddler or ask your spouse or other caregivers, where possible.*
- *Depending upon the age of your child not all items will apply; mark N/A (not applicable) if the item is too advanced for your child's age.*

SCORING

- *A score or 1 indicates that you have no concern about the behavior and you feel that the infant is developing typically*
- *A score of 2 indicates a mild problem, i.e., child's behaviour is not completely typical of what you expect of his/her age*
- *A score of 3 indicates a moderate problem i.e., child behaviour is concerning, but not as severe as described in (4)*
- *A score of 4 indicates a severe problem that matches one or more of the descriptions provided*

	No evidence of difficulty 1	**Mild problem 2** **Moderate problem 3**	**Severe problem 4**
1.	NAP TIME Sleeps well at nap time; wakes easily on his/her own	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Difficult to wake especially for feedings; or excessively light sleeper, need to tip-toe around during infant's nap time
	Comments:		
2.	SLEEP DURTION AT NIGHT Sleeps at least four hours consecutively during the night; easy to get back to sleep	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Wakes frequently during the night; stays awake for long periods during the night
	Comments:		
3.	SLEEP DURATION TOTAL PER DAY Sleeps at least 10 hours per day (night-time and naps combined)	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Sleeps less than 10 hours per day (night-time and naps combined)
	Comments:		
4.	ACCEPTS BOTTLE/BREAST FEEDING Accepts breast or bottle-feeding readily	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Has difficulty sucking, or resists or appears to lose interest in feeding

	Comments:		
5.	MILK/FORMULA TOLERANCE Tolerated breast milk or formula well; rarely spit up mild or formula	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Could not tolerate breast milk or formula; spit up frequently; needed milk substitute (e.g. soy)
	Comments:		
6.	ACCEPTANCE OF NEW FOODS Accepts transition to *new* food readily, e.g., breast to bottle, pablum to puree, new tastes, new textures	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Strongly resists switch to bottle feeding or introduction of pablum/baby food; strongly resists/refuses new tastes and/or textures
	Comments:		
7.	APPETITE Enjoys a variety of foods and eats an appropriate amount for child's age	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Eats and/or drinks small quantity and/ or variety; or has a huge appetite, eats a lot more than expected for his/her age, always wanting food
	Comments:		
8.	CUDDLING Accepts and enjoys cuddling and physical affection	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Actively resists being cuddled; dislikes being touched or picked up; or passive, indifferent to being picked up
	Comments:		
9.	DEMANDS PARENT ATTENTION Cries or vocalizes and looks for parent when parent leaves room or parent is occupied	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Appears indifferent to parent attention; prefers to be left alone most of the time
	Comments:		
10.	MOOD Easy to please; generally good mood; appears to be a happy child	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Difficult to please; frequent colic symptoms; appears to be unhappy and/or irritable child
	Comments:		
11.	SMILING Readily smiles at people during social interactions	**1**------1.5------**2**------2.5------**3**------3.5------**4**	No social smile; might smile during play but not directed at people
	Comments:		
12.	LAUGHING Laughs readily in social situations; responds to other's laughter	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Never laughs in social situations; may appear unaware of or indifferent to other's laughter; may laugh only when alone; other's can't figure out why
	Comments:		
13.	ATTACHMENT TO PARENTS Differentiates parents from other adults; may be shy with	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not differentiate parents from other adults; would happily go to or stay with an adult; does not acknowledge parent's

	strangers; cries when left with less familiar adult		leaving the room
	Comments:		
14.	RECOGNITION OF PARENT'S VOICE Turns head toward mother or father's voice when held by another adult	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not appear to differentiate parent's voice from that of a stranger; no turning to look for parent when child hears parent's voice
	Comments:		
15.	PAIN REACTION Reacts to painful event (e.g., fall, cut) by crying or screaming; recovers quickly from mild bumps or discomfort	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not appear to feel pain in situations when others would find painful; or overreacts to what should be mild bumps or discomfort
	Comments:		
16.	SEEKS COMFORT WHEN HURT Seeks adult comfort when hurt; able to calm down when comforted	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not seek out adults when hurt; actively resists comforting when adult initiates; or difficult to calm when upset
	Comments:		
17.	APPROPRIATENESS OF EMOTIONS Crying or laughter is appropriate to the situation	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Displays apparently unmotivated fits of crying or laughter; frequently can't figure out what he/she's crying or laughing about
	Comments:		
18.	ANTICIPATION TO BEING PICKED UP Shows excitement or anticipation when being picked up; raises arms to adult	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Shows no awareness or anticipation of being picked up; does not raise arms to be picked up
	Comments:		
19.	CONSISTENCY OF RESPONSE Shows consistent response to familiar people, situations or places; easy to predict what will please or upset	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Highly inconsistent response to familiar people, situations, or places; difficult to predict reaction; small changes can set off and upset
	Comments:		
20.	TOLERANCE OF TRANSITIONS Accepts transitions from one activity to another easily (e.g., play to meal or bath time)	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Usually becomes very upset during transitions; may tantrum or cry for prolonged period
	Comments:		
21.	ATTENTION TO LOUD NOISE Turns head toward loud noise right away	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not respond to loud noises appears not to hear; or is overly reactive to loud noises and startles easily
	Comments:		
22.	RESPONSE TO NAME	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not respond to name when

	Responds to name by turning eyes and head toward person calling name; prefers human voice over object noise		called; does not look at the caller; may appear deaf to the human voice
	Comments:		
23.	EYE CONTACT Makes eye contact easily during feeding, bathing etc.	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Never makes eye contact; avoids eye contact all the time
	Comments:		
24.	INTEREST IN OBJECTS Shows interest in objects that move or make noises	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Is excessively fearful of and tries to avoid certain object that move or make noises (e.g., fans, vacuums)
	Comments:		

25.	VISUAL TRACKING-SIDE TO SIDE Good visual tracking of an interesting object moved slowly side to side	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not track objects at all when object is slowly moved from side to side
	Comments:		
26.	VISUAL TRACKING-UP AND DOWN Good visual tracking of an interesting object moved slowly up and down	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not track objects at all when object is moved slowly up and down
	Comments:		
27.	INTEREST IN FACES Shows more interest in a person's face than in objects/toys	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Prefers looking at objects/toys' indifferent to faces or avoids faces
	Comments:		
28.	SHIFTS ATTENTION TO PERSON Shifts attention from object/toy to person's face easily	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Has great difficulty shifting attention from an object/toy to a face
	Comments:		
29.	SHIFTING ATTENTION BETWEEN EVENTS Shifts attention readily from one toy or event to another	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Gets "stuck" on one toy or activity and may not even notice when another toy or activity is introduced
	Comments:		
30.	OBJECT PERMENANCE Searches for object/toy when hidden by adult or lost from view	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Immediately loses interest when object/toy is out of view, does not search for lost object/toy
	Comments:		
31.	MUSCLE TONE Shows good muscle tone when sitting, rolling, crawling, or grasping objects	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Shows very poor muscle tone when sitting or moving; floppy baby; rarely initiates movement
	Comments:		
32.	AGILITY IN MOVEMENT	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Awkward in moving; may adopt

	Developmentally appropriate movement: crawls, walks, runs, climbs smoothly		unusual postures or gait (e.g., toe-walking); appears to move like a younger child
	Comments:		

33.	EXPLORING NEW ENVIRONMENTS Enjoys exploring new environments and new toys	1------1.5------2------2.5------3------3.5------4	Shows no interest in new places or new toys; or actively tries to leave new place or discard new toy
	Comments:		
34.	APPROPRIATE TOY PLAY Plays appropriately with toys; explores, uses toy as intended	1------1.5------2------2.5------3------3.5------4	Plays inappropriately wit toys; throws, destroys, plays with just one part not as intended; highly repetitive and stereotyped play
	Comments:		
35.	ATTENTION SPAN Plays with toys for amount of time appropriate to age (several minutes in infancy; gradually expanding with age to 15-30 min by age 2)	1------1.5------2------2.5------3------3.5------4	Attention is much briefer than expected given child's age; only able to focus for longer periods on TV, video, or limited set of objects of special interest
	Comments:		
36.	RANGE OF INTEREST IN TOYS Shows interest in variety of toys appropriate of child's age	1------1.5------2------2.5------3------3.5------4	Very limited range of interest in only one or two objects or toys not always appropriate to age
	Comments:		
37.	TOY VS. BODY PLAY Prefers to play appropriately with toys on own or with other	1------1.5------2------2.5------3------3.5------4	Prefers to lay with his/her own body, using whole body movements (e.g., spinning, rocking) or small body movement (e.g., hand gazing, flapping)
	Comments:		
38.	BUILDING TOWERS Builds towers with at least 3 blocks without adult assistance	1------1.5------2------2.5------3------3.5------4	Can not build tower even with adult assistance; shows no interest and may resist tower building
	Comments:		
39.	IMITATES ACTIONS Readily imitates actions of others with toys or imitates body actions when asked "to this".	1------1.5------2------2.5------3------3.5------4	Never imitates action of others with toys or body actions of others when asked "to this".
	Comments:		
40.	IMITATES SOUNDS OR WORDS Readily imitates sounds or words of others, spontaneously or when asked "say ___"	1------1.5------2------2.5------3------3.5------4	Never imitates sounds or words of others, spontaneously or when asked "say ___"
	Comments:		

41.	PRETEND PLAY	**1**------1.5------**2**------2.5------**3**------3.5------**4**	No evidence of pretend play;

	Able to pretend play, as in making tea in toy cup, feeding doll with spoon, pushing toy car with appropriate sounds		may use toy cups or spoons as if real; may push car without sounds or pretend actions; no evidence that child is pretending
	Comments:		
42.	ACTIVITY LEVEL Shows appropriate activity level during unstructured play	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Appears lethargic or overly passive during unstructured play; or is overly excited and hyperactive during unstructured play
	Comments:		
43.	CRIES/VOCALIZES TO EXPRESS NEEDS Easily expresses needs with cries and vocalizations (hungry, wet, soiled or sleepy)	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not appear to be aware of own needs; does not cry when hungry or in discomfort
	Comments:		
44.	SOCIAL GAMES Enjoys playing social games (e.g., peek a boo, being swung, bounce on adult knee, songs, chase, ring-around- the-rosy)	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Indifferent to or avoids social games; resists by looking away, pushing away, or moving away when game initiated by others
	Comments:		
45.	POINTING TO REQUEST Uses index finger to point to ask for something; may use words along with point	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not point to make request; may use whole hand to reach toward the object of interest
	Comments:		
46.	POINTING TO SHARE INTEREST Uses index finger to point to indicate interest in something out of reach	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not point to interesting object to direct your attention; may look toward or reach toward
	Comments:		
47.	COORDINATES POINT AND GAZE When pointing to something child wants, checks that adult is looking in same direction	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Point toward object he/she wants, but does not check to make sure adult is looking
	Comments:		
48.	POINTS IN RESPONSE TO QUESTIONS When asked "Where's the light (or other object out of reach)?" points with full hand reach or, later with index finger	**1**------1.5------**2**------2.5------**3**------3.5------**4**	When asked a where question, does not look toward object; never attempts to point to or each toward the object requested
	Comments:		

49.	FOLLOWS ADULT POINT WITH GAZE Looks toward an object when the adult points and says	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not turn head in direction of adult point when adult points and says "Look there's a _____!"

	"look, there's ____!"		
	Comments:		
50.	FOLLOWS SIMPLE DIRECTION When asked to do something simple, can respond appropriately when adult does not point (get your shoes, give me the dolly)	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Not able to understand or follow any adult direction unless adult uses gestures or physically prompts the child to follow through
	Comments:		
51.	INTEREST IN BIRTHDAYS/PRESENTS Shows interest or excitement when he/she or sibling given birthday cake or present	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Appears indifferent when given a birthday cake or presented with a present
	Comments:		
52.	BRINGING TOY TO REQUEST Brings toys/objects over to adult to request assistance or permission	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Never brings toys or objects to an adult to request assistance or permission
	Comments:		
53.	BRINGING TOY TO SHARE ATTENTION Bring toys/objects over to adult to show or share joint attention	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Never brings toys to show adult or to share going attention
	Comments:		
54.	WAITING Tolerates brief wait before needs can be met; remains calm but expectant while waiting	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Cannot tolerate any wait to have needs met; easily frustrated; quick to cry or tantrum if needs are not met immediately
	Comments:		
55.	WAVES BYE-BYE Waves bye-bye when someone is leaving the home, without prompts to wave	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Indifferent to visitors leaving; may resist prompts to wave bye-bye
	Comments:		

56.	GREETINGS Acknowledges parents after brief period of absence with unprompted approach to smile, give or receive a hug, and/or says "hi"	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Indifferent to parents when returning after period of absence; does not acknowledge with greeting, smile or hug; may resist parent's greeting.
	Comments:		
57.	INTEREST IN PEERS Shows interest in the play of other children or siblings; watches other children playing	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Shows no interest in the activity of other children; ignores them as if they were not present
	Comments:		
58.	PLAY WITH PEERS Appropriate level of	**1**------1.5------**2**------2.5------**3**------3.5------**4**	No interest in playing with or near siblings or peers; may do

	engagement with play side by side with same set of toys)		some chase or tickles with sibs, but won't share toys or materials; moves away from peers/sibs
	Comments:		
59.	COORDINATE GESTURES WITH COMMUNICATION Expresses needs easily by combining gestures and vocalizations or speech	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Frequently frustrated in communicating needs; resorts to screaming, crying, tantrums, etc.; or does not persist, walks away when not understood the first time
	Comments:		
60.	COMMUNICATES WITH WORDS Consistently uses understandable words to communicate needs and interests	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Does not have any words to express needs or interests; uses gestures and vocalizations only
	Comments:		
61.	CONVENTIONAL USE OF WORDS Uses conventional. common words or phrases to express needs and interest	**1**------1.5------**2**------2.5------**3**------3.5------**4**	Uses a lot of idiosyncratic, echolalic or made-up words and phrases to express needs and interests